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Synthesis of Ambrox® from labdanolic acid

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Abstract—A synthesis of the valuable amber-type odorant Ambrox® from labdanolic acid (main diterpenoid of the acid fraction of non-polar extracts of *Cistus ladaniferus* L.) is reported. The conversion is based on (a) the α,β-dehydrogenation of methyl labdanolate using an organoselenium reagent, (b) subsequent oxidative degradations of the side chain, and (c) final acid-promoted cyclization of the resulting tetranorlabdan-8α,12-diol. The influence of the temperature and solvent in the cyclization of the diol with *p*-toluenesulfonic acid is also described. Thus, Ambrox® has been obtained by a six-step procedure in 33% overall yield from methyl labdanolate. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Since Ambrox® (**1**)[†] was initially prepared in 1950 from (−)-sclareol[1,2] considerable synthetic work has been done to obtain this valuable amber odorant.[3–15] One of the reasons for the steady interest is that **1** still remains the prototype of what perfumers understand as an ambery note.[16] It possesses the character of the no longer used natural ambergris and it plays a central role in fragrance creations. Thus, nowadays, a considerable world consumption of this synthetic material exists. It is also known that diterpene (−)-sclareol still constitutes the only practical starting material for the industrial preparation of **1** and, therefore, the available quantity of Ambrox® is limited, and its price accordingly high.[3d] This is another reason why efforts have been concentrated on the search of new syntheses starting from cheap and abundant alternative natural products. In fact, several syntheses of Ambrox® have been developed from diterpenoids such as (−)-manoyl oxide,[17] (−)-abietic acid,[18] (−)-levopimaric acid,[19] (+)-communic acids,[20,21] (+)-*cis*-abienol[22] and (−)-labda-12,14-dien-7α,8α-diol,[11] from sesquiterpenoids such as (−)-drimenol,[23,24] and also from monoterpenoids such as (+)-carvone[25] and thujone.[7] In addition to these compounds, the diterpene (−)-labdanolic acid (**2**) is a suitable chiral synthon for the synthesis of **1**, because of its structural features and easy availability from Nature. It has been found in different plants[26–28] and it is the main component of the acidic fraction of non-polar extracts of *Cistus ladaniferus* L.,[29–31] an abundant and widely distributed plant in the Iberian Peninsula.[32] Labdanolic acid[33] and its methyl ester[34,35] have already been converted into norambreinolide, a classic precursor of Ambrox®,[3b] through an oxidative cyclization with lead tetraacetate. Later, the 8-acetyl derivative of labdanolic acid was converted into norambreinolide and ambroxdiol (another precursor of Ambrox®), through an oxidative decarboxylation reaction promoted by lead tetraacetate/copper(II) acetate.[36]

In this paper, we report on the synthesis of Ambrox® (**1**) from labdanolic acid (**2**) based on the α,β-dehydrogenation of methyl labdanolate (**3**), subsequent oxidative degradation of the side chain and final stereoselective formation of the tetrahydrofurane ring (Scheme 1). While preparing this manuscript, a formal synthesis of Ambrox from labdanolic acid, by iododecarboxylation of 8-acetyl-labdanolic acid with iodobenzenediacetate, had been published in this journal.[37]

2. Results and discussion

The starting material for the synthesis of Ambrox® (**1**) was obtained from an ethereal extract of wild-grown *C. ladaniferus*, harvested on the northwest of Jaén province. An extract was prepared by simple soaking of the plant material in Et_2O for 1 day at room temperature. It was then dewaxed and fractionated to afford an acidic fraction from which labdanolic acid (**2**) was isolated by chromatography. The treatment of this acidic fraction with diazomethane gave a mixture of methyl esters that was purified by chromatography to afford pure methyl labdanolate (**3**) in 43% yield. For comparison, this isolation procedure of **3** was applied to a plant material extracted with *n*-hexane in a Soxhlet apparatus as usual.[38] The isolated yield of **3** was similar in both cases but we found that a simple extraction of the plant with cold Et_2O was more convenient than a

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Keywords: Ambrox®; labdanolic acid; α,β-dehydrogenation; oxidative degradations; stereoselective cyclization.

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[†] Registered trademark of Firmenich S.A. for (−)-8α,12-epoxy-13,14,15,16-tetranorlabdane.

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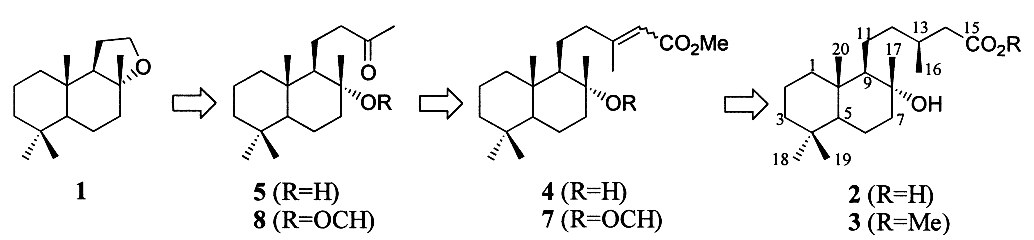
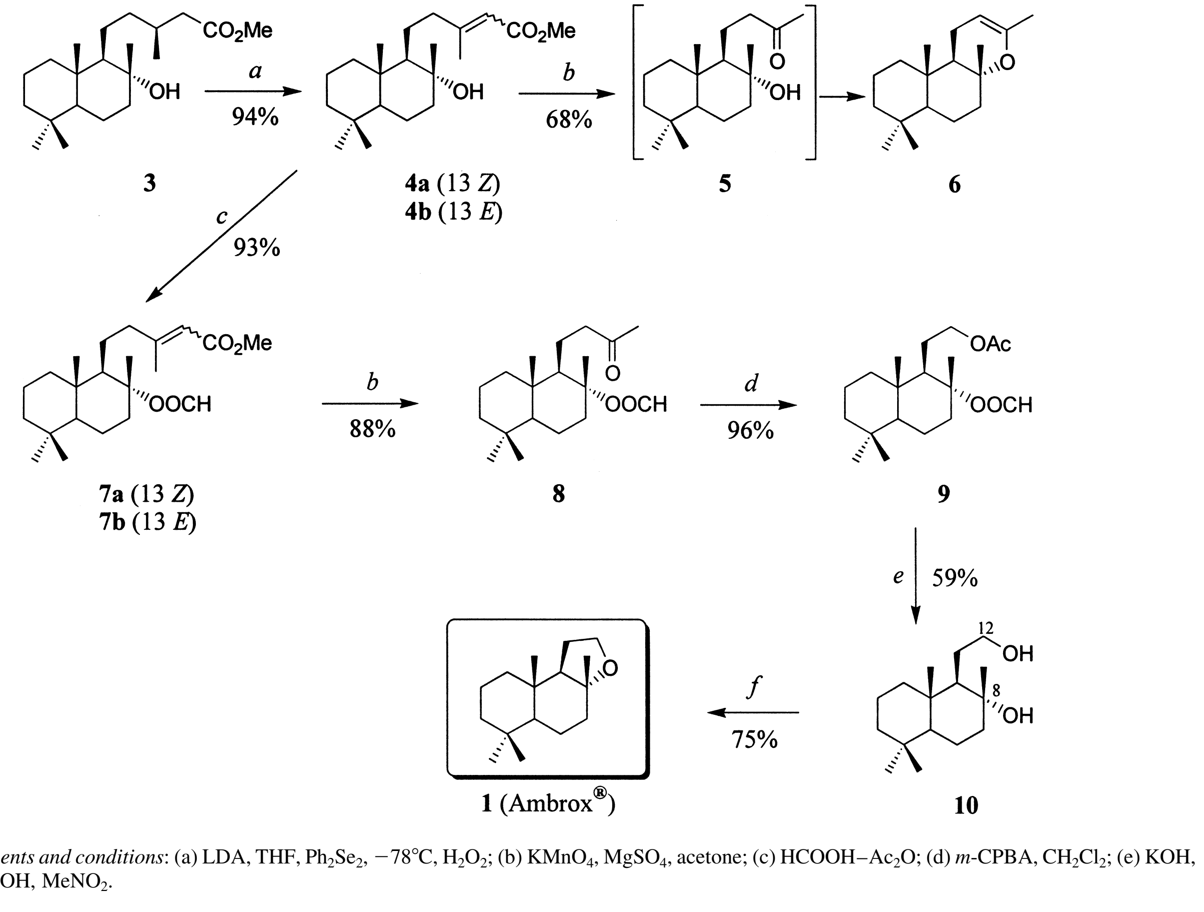


Scheme 1. Retrosynthetic analysis of Ambrox® (**1**) from labdanolic acid (**2**).

continuous extraction with *n*-hexane. In addition, the application of that purification protocol to a labdanum gum sample assured us that the commercial product of rock-rose does not contain the desired compound **3**.

As shown in Scheme 1, the degradation of the side chain of methyl labdanolate (**3**) was achieved in two steps: (1) cleavage of the C_{13}–C_{14} bond, the initial formation of a Δ^{13} double bond being needed, and (2) cleavage of the C_{12}–C_{13} bond, via Baeyer–Villiger reaction carried out on the resulting methyl ketone. For performing the α,β-dehydrogenation of compound **3**, the method of Sharpless and co-workers[39] was chosen to prepare the α,β-unsaturated esters with electrophilic organoselenium reagents.[39–41] Thus, compound **3** was treated with 2 equiv. of lithium diisopropilamide (LDA), and then with other 2 equiv. of Ph_2Se_2 at low temperature. The resulting α-phenylseleno esters were oxidized with hydrogen peroxide to give spontaneous elimination of benzeneselenenic acid at room temperature giving mixtures of the α,β-unsaturated esters **4a** and **b** (Scheme 2). The use of hexamethylphosphoramide in the selenenylation step improved the yields,[40,42] allowing the conversion of **3** into **4a** and **4b** in 94% yield (55:45 ratio acc. GC). Alternatively, the α,β-dehydrogenation of compound **3** was proved with the cheaper diphenyl disulfide.[43] However, the need to heat for the dehydrosulfenylation resulted in the undesired loss of the tertiary hydroxyl group. This and the fact that the reaction of **3** with Ph_2Se_2 had the added interest of allowing the recovery of the reagent in good yields by reduction of the by-product benzeneseleninic acid,[41] made the procedure most appropriate for the preparation of compounds **4a** and **b**.

Treatment of the α,β-unsaturated esters **4a/b** with $KMnO_4$ in acetone or THF/water mixtures[44] for several hours afforded the methyl ketone **5**, which tended to cyclize to sclareol oxide (**6**). The addition of anhydrous $MgSO_4$ to the reaction mixture in acetone[45] efficiently shortened the reaction times allowing the conversion of **4a/b** into a mixture of **5** and **6** (5:2 ratio) in 30 min (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) LDA, THF, Ph_2Se_2, −78°C, H_2O_2; (b) $KMnO_4$, $MgSO_4$, acetone; (c) HCOOH–Ac_2O; (d) *m*-CPBA, CH_2Cl_2; (e) KOH, MeOH; (f) *p*-TsOH, $MeNO_2$.

Table 1. Cyclization reactions of **10** with *p*-toluenesulfonic acid under different experimental conditions

Entry	**10**[a] (mmol)	*p*-TsOH (mmol)	$MeNO_2$ (mL)	CH_2Cl_2 (mL)	Temperature	Reaction time (h)	Products distribution (%)[b]					
							10	**1**	**11**	**12**	**13**	**Others**
1	0.28	0.17	5	–	r.t. (~20 °C)	1	–	87.1	–	9.8	1.5	–
2	0.28	0.17	5	–	r.t. (~20 °C)	2	–	88.5	–	8.3	1.1	–
3	0.28	0.17	5	–	r.t. (~20 °C)	3	–	87.7	t	9.1	1.1	–
4	0.28	0.17	5	–	r.t. (~20 °C)	7	–	83.5	2.5	10.5	1.5	–
5	0.28	0.17	5	–	r.t. (~20 °C)	24	–	83.8	5.7	7.1	1.2	t
6	0.28	0.17	5	–	r.t. (~20 °C)	96	–	71.0	16.1	6.4	1.1	2.6
7	0.04	0.03	–	1	r.t. (~20 °C)	1	10.4	65.2	–	16.8	7.6	–
8	0.04	0.03	–	1	r.t. (~20 °C)	3	t	83.8	–	11.2	4.9	–
9	0.04	0.03	–	1	r.t. (~20 °C)	21	–	88.7	–	11.3	t	–
10	0.29	0.18	5	–	80–85°C[c]	0.5	–	11.9	38.7	6.9	1.1	41.4
11	0.29	0.18	5	–	80–85°C[c]	1	–	t	32.9	t	t	67.1
12	0.29	0.18	5	–	80–85°C[c]	2	–	–	36.9	–	–	63.2
13	0.29	0.18	5	–	80–85°C[c]	3	–	–	37.1	–	–	62.9
14	0.29	0.18	5	–	80–85°C[c]	21	–	–	23.6	–	–	76.4
15	0.29	0.18	5	–	80–85°C[c]	30	–	–	17.8	–	–	82.3
16	0.28	0.17	–	5	reflux	0.5	8.6	67.4	–	16.8	7.2	–
17	0.28	0.17	–	5	reflux	1	–	85.9	–	11.9	2.1	–
18	0.28	0.17	–	5	reflux	2	–	84.5	3.0	10.5	2.0	–
19	0.28	0.17	–	5	reflux	3	–	86.3	5.4	7.4	0.9	–
20	0.28	0.17	–	5	reflux	30	–	29.6	59.1	11.2	t	t

[a] Starting material.

[b] Percentages deduced from the GC analysis of the crude reactions; t means traces.

[c] Oil bath temperature.

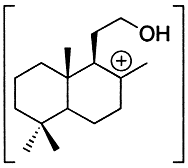
Attempts to separate both compounds by chromatography on silica gel failed as only the cyclized **6** was eluated by chromatography in 68% yield.

Aware of the difficulties to isolate methyl ketone **5** and the impossibility to carry out the planned Baeyer–Villiger on it, we decided to prevent the interference of the hydroxyl group at C-8 by protection as acetate. Thus, a mixture of **4a/b** was treated with Ac_2O, triethylamine and *N*,*N*-dimethylaminopyridine (DMAP) for several days, with further additions of Ac_2O and DMAP. However, an unexpected low yield was observed. Supposing a hindering effect of the side chain, a less-hindered protecting group was chosen. The reaction of compounds **4a/b** with formic acid–acetic anhydride mixture (FAM)[46] afforded the formyl derivatives **7a/b** in 93% yield. These were directly oxidized with $KMnO_4$ to give the corresponding methyl ketone **8** in 88% yield (Scheme 2).

The Baeyer–Villiger reaction on compound **8** with *m*-chloroperoxybenzoic acid (*m*-CPBA) at room temperature led to the desired acetoxy derivative **9** in 96% yield. In order to avoid long reaction times, a modified procedure based on the use of mixtures of trifluoroacetic acid (TFA) and *m*-CPBA was followed.[47] Reaction times were shorter than before, but side products were observed now, which could be circumvented by the addition of phosphate buffer to the reaction mixture (Method B in Section 3.3.4). The reaction of **9** with a methanol/KOH solution afforded the diol **10** (59% yield), which was conveniently cyclized with *p*-toluenesulfonic acid (*p*-TsOH) in nitromethane at room temperature to give Ambrox (**1**) in 75% yield after chromatographic purification (Scheme 2).

Several approaches to transform the diol **10** into **1** have been reported in the literature. They are based on the treatment of **10** with reagents such as tosyl chloride, phosphorous oxychloride, zinc halides, aluminum oxide-based catalysts or sulfonic acids. The cyclization of **10** is a delicate step as the configuration at C-8 has to be retained. A way to avoid epimerization at that stereocenter is to favor the intramolecular nucleophilic substitution of the tertiary hydroxyl group over the primary at C-12, which can be easily accomplished by converting the primary hydroxyl group in a good leaving group by reaction of **10** with *p*-toluenesulfonyl (or methylsulfonyl) chloride in pyridine.[10,22,48] However, this effective method has the laborious elimination of the bad-smelling pyridine as its main drawback, although an efficient replacement of pyridine by other odorless bases is already known.[8] In addition, acidic reagents can be employed. It is assumed[49] that these acid-catalyzed cyclization reactions proceed by attack of the primary hydroxyl group on the tertiary carbocation **I**. This means that the risk of epimerization at C-8 remains, as the α-face attack affords Ambrox (**1**) and the β-face attack gives *iso*-Ambrox (**11**). *p*-Toluenesulfonic acid in nitromethane has been one of the most often used systems.[7,9,20,37,49–51] However, a minor discrepancy concerning the suitable temperature at which the experiment has to be carried out still exists as both low[20,37,50,51] and high[7,9,49] temperature procedures seem to give Ambrox. Our previous experience[20] on the cyclization of the 8-*epi* diol **II** with *p*-TsOH/$MeNO_2$ showed that low temperatures favored the equatorial approach of HO–C-12 to the tertiary carbocation while high temperatures promoted the axial approach, which agrees with the known statement[1,2] that Ambrox (*trans*-fused tetrahydrofuran ring) is the kinetic isomer, and *iso*-Ambrox (*cis*-fused tetrahydrofuran ring) the thermodynamic one. In order to examine the influence of the temperature and solvent on the cyclization of the diol **10** with *p*-TsOH, a series of experiments have been carried out

(Table 1). The reaction of **10** with *p*-TsOH/$MeNO_2$ at room temperature (entries 1–6) afforded reaction mixtures mainly composed of **1** along with minor amounts of **11** (entries 3–6) and alkenols **12** and **13**, the latter compounds being identified by GC–MS analysis. Mixtures of these olefinic alcohols have also been detected in similar studies on **10** and a related stereoisomer.[7] It can be seen how *iso*-Ambrox (**11**) gradually increases with longer reaction times (entries 3–6). It is thus expected that **11** will become the major product under prolonged treatments. When $MeNO_2$ was replaced by a less polar solvent such as CH_2Cl_2 (entries 7–9) and the reactions were carried out at room temperature a similar steroselectivity in the cyclization was observed. In addition, a marked decrease in the rate of the process was noted, a reaction time of 21 h being required (entry 9) to get a comparable yield to that obtained with $MeNO_2$ after 2 h (entry 2). However, the treatment of **10** with *p*-TsOH/$MeNO_2$ at 80–85°C (entries 10–15) led to crude reactions where **11** appears in higher percentage than **1** (entry 10). In addition, a successive decrease of **11** (and **12** and **13**) in favor of other unidentified components was observed under prolonged reaction times. These components could not be purified and studies to clarify their identity were not pursued. Finally, when **10** was refluxed with *p*-TsOH/CH_2Cl_2 (entries 16–20), a stereoselective formation of **1** was still observed after 1 h reaction time (entry 17) whereas it was lost in favor of **11** under longer reaction times (entry 20). This allowed us to deduce that the stereoselective acid-promoted cyclization of the diol **10** to Ambrox (**1**) can be efficiently accomplished both at room temperature (entries 2 and 9) and at high temperature (entry 17) in regard of the solvent chosen; either $MeNO_2$ or CH_2Cl_2 in the first case or CH_2Cl_2 in the second one.



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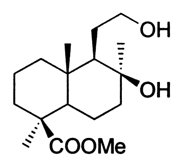

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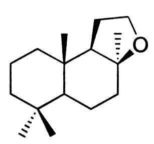

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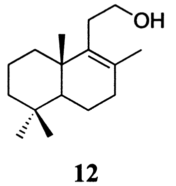

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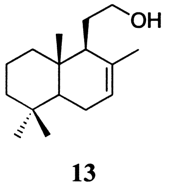

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In conclusion, a novel route to Ambrox® has been developed from an abundant natural product via a six-step procedure in 33% overall yield. All reactions of this synthesis were carried out with crude materials. Because of the potential interest of this starting material for the industrial preparation of Ambrox®, further work is in progress.

3. Experimental

3.1. General and instrumentation

Reactions with exclusion of moisture were performed with pre-dried glassware under a positive pressure of argon. Commercial reagent grade chemicals and solvents such as Et_2O and $MeNO_2$ were used as received, unless otherwise stated. THF was freshly distilled from sodium benzophenone ketyl under argon and the hexane (H) and ethyl acetate (EtOAc), used for chromatographic separations, and MeOH, acetone and CH_2Cl_2, used as solvents, were glass-distilled prior to use. Reactions were monitored by gas chromatography (GC) and/or analytical thin-layer chromatography (TLC) and the reaction products were purified by conventional column chromatography (Merck silica gel 60, 70–230 mesh) using hexane/Et_2O (H/E) mixtures of increasing polarity, or by flash chromatography (Scharlau silica gel 60, 230–400 mesh) using the appropriated H/E mixture, with air pressure to obtain a suitable flow. These column chromatographic separations were monitored by GC and/or TLC. Analytical TLC was performed using Merck precoated (0.25 mm) silica gel 60 F_{254} aluminum-backed TLC plates, and compounds were visualized by UV light and by spraying with a 10% solution of phosphomolybdic acid in ethanol followed by heating until blue spots developed. GC analyses were performed on a Varian CP-3800 gas chromatograph fitted with a methyl silicone (CP-Sil 8 CB) capillary column (30 m×0.25 mm×0.25 μm); carrier gas: He; flow rate: 1 mL/min; oven temperature program: 100–290°C at a rate of 8°C/min; injector temperature: 250°C; flame ionization detector temperature: 300°C; retention times (R_t) are expressed in minutes. Melting points (mp) were determined on an Electrothermal 9300 melting point apparatus and are uncorrected. Optical rotations ($[\alpha]_D$) were recorded on a Perkin–Elmer 241 automatic polarimeter using quartz cells of 1 dm path length, in $CHCl_3$ solutions; concentration (*c*, expressed in cg/mL) is given in parentheses. Infrared (IR) spectra were recorded on a FT-IR Perkin–Elmer 1760X spectrometer using a thin film between KBr plates (neat) or as KBr pellets; only characteristic absorptions (ν, cm^{-1}) are reported. ^1H NMR spectra were recorded at 300 MHz on a Bruker DPX 300 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference; chemical shift values are reported in parts per million (ppm, δ scale) and coupling constants (*J*) are in hertz (Hz); multiplicity of signals are expressed as s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet, br s: broad singlet, dd: double doublet, ddd: double double doublet, dt: double triplet and td: triple doublet. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument; chemical shifts are reported in ppm relative to TMS; carbon substitution degrees were established by DEPT multipulse sequence. 2D NMR experiments (DQF-COSY, HSQC, HMBC) were carried out for compounds **6**, **7a** and **b** on the same instrument. Mass spectra (MS) were recorded on a Hewlett–Packard 5989B mass spectrometer using the electron impact ionization method (70 eV); MS were obtained in most cases by GC–MS analysis carried out on a Hewlett–Packard 5890A II gas chromatograph coupled to the mass spectrometer described above; the parameters for the GC unit were the same than those described previously for the GC analyses; ion source temperature of the MS unit: 250°C; scan range from *m*/*z* 35 to 400; the ratios *m*/*z* and relative intensities (%) are indicated for the significant and major peaks. High-resolution mass spectra (HRMS) were recorded on a Micromax VG Autospec spectrometer.

3.1.1. Labdanolic acid (2). Air-dried twigs of *C. ladaniferus* L. (904.03 g), harvested in May 1999 in the Sierra de Andújar Natural Park (province of Jaén, Spain), were pieced and soaked in Et_2O at room temperature for 24 h. The solution was removed from the plant material and the solvent was evaporated under reduced pressure to give an extract (84.91 g), which was dewaxed with MeOH (16.94 g) and by formation of urea clathrate compounds (0.73 g). The resulting extract was re-solved in Et_2O and washed with a 10% aq. Na_2CO_3 solution (3×150 mL) to give a neutral fraction (23.85 g) and an acid fraction (34.05 g). An aliquot sample (4.68 g) of this acid fraction was purified by conventional column chromatography (eluents: from H to H/EtOAc 4:6) to give **2** (1.40 g) as a sticky solid (lit.[37]); $[\alpha]_D=-6.6°$ (*c* 1.06); IR (neat) ν 3600–2500, 1708 (COOH), 3408, 1083 (OH); ^1H NMR δ 0.78 (6H, s, Me_β-4, Me-10), 0.86 (3H, s, Me_α-4), 0.98 (3H, d, *J*=6.6 Hz, Me-13), 1.15 (3H, s, Me-8), 1.85 (1H, dt, *J*=12.3, 3.3 Hz, H_β-7), 2.19 (1H, dd, *J*=14.8, 7.2 Hz, H-14), 2.30 (1H, dd, *J*=14.8, 6.4 Hz, H′-14); ^{13}C NMR δ 39.58 (C-1), 18.38 (C-2), 41.94 (C-3), 33.16 (C-4), 55.96 (C-5), 20.37 (C-6), 43.74 (C-7), 74.92 (C-8), 61.97 (C-9), 39.04 (C-10), 22.99 (C-11), 40.45 (C-12), 31.15 (C-13), 41.49 (C-14), 177.87 (C-15), 19.89 (C-16), 23.79 (C-17), 33.33 (C-18), 21.43 (C-19), 15.45 (C-20); MS *m/z* 324 (M^+, 1%), 306 (M^+-H_2O, 4), 291 (M^+-H_2O-Me, 7), 266 (1), 253 (3), 235 (9), 217 (4), 193 (5), 171 (21), 153 (15), 137 (13), 123 (24), 109 (27), 95 (30), 81 (36), 69 (79), 55 (74), 43 (100).

3.1.2. Methyl labdanolate (3). A sample (29.37 g) of the acid fraction prepared as described in Section 3.1.1 from *C. ladaniferus* extract was treated with an ethereal diazomethane solution, generated in situ by adding a methanolic 2N KOH solution (175 mL) over a suspension of *N*-methyl-*N*-nitrosotoluene-4-sulfonamide (40.30 g) in Et_2O (400 mL). The resulting mixture of methyl esters (30.41 g) was purified by conventional column chromatography (eluents: from H to H/E 6:4) to give **3** (12.75 g) as light green crystals (lit.[38]); R_t 20.54; mp 68.3–71.3°C (hexane); $[\alpha]_D=-8.0°$ (*c* 1.11); IR (neat) ν 3483, 1085 (OH), 1739, 1260, 1201, 1160 (COOMe); ^1H NMR δ 0.78 (6H, s, Me_β-4, Me-10), 0.86 (3H, s, Me_α-4), 0.95 (3H, d, *J*=6.7 Hz, Me-13), 1.14 (3H, s, Me-8), 1.86 (1H, dt, *J*=12.0, 3.1 Hz, H_β-7), 2.16 (1H, dd, *J*=14.6, 8.0 Hz, H-14), 2.34 (1H, dd, *J*=14.6, 5.8 Hz, H′-14), 3.66 (3H, s, OMe); ^{13}C NMR δ 39.59 (C-1), 18.37 (C-2), 41.90 (C-3), 33.15 (C-4), 56.01 (C-5), 20.43 (C-6), 44.16 (C-7), 74.13 (C-8), 62.15 (C-9), 39.01 (C-10), 22.74 (C-11), 40.60 (C-12), 31.21 (C-13), 41.35 (C-14), 173.83 (C-15), 19.83 (C-16), 23.91 (C-17), 33.33 (C-18), 21.42 (C-19), 15.42 (C-20), 51.35 (OMe); MS *m/z* 338 (M^+, 0.3%), 320 (M^+-H_2O, 0.7), 307 (M^+-OMe, 0.5), 305 (M^+-H_2O-Me, 1), 267 (1), 235 (2), 217 (1), 191 (1), 185 (3), 177 (5), 153 (4), 144 (16), 125 (24), 109 (26), 101 (31), 95 (25), 81 (36), 69 (83), 55 (73), 43 (100).

3.2. Reaction of 3 with Ph_2Se_2/H_2O_2 to give α,β-unsaturated ester derivatives 4a and b

To a stirred solution of dry $^iPr_2NH$ (2.4 mL, 17.10 mmol, distilled from CaH_2 and stored over molecular sieves) and dry THF (36.0 mL) was added dropwise a 2.5 M solution of *n*-BuLi in hexane (6.0 mL, 15.00 mmol) at −78°C under argon. After stirring for 0.7 h at −78°C a solution of **3** (2.03 g, 6.00 mmol) in dry THF (18.0 mL) was added dropwise. The mixture was allowed to stir for 1 h at the same temperature and, then, a solution of Ph_2Se_2 (4.50 g, 14.40 mmol) in dry HMPA (7.0 mL, stored over molecular sieves) was slowly poured into. After further stirring for 1 h at −78°C, the mixture was allowed to warm to room temperature and a saturated aq. NH_4Cl solution (40 mL) was added. The mixture was extracted with Et_2O (3×50 mL) and the combined organic layers were washed with 2N HCl (50 mL), saturated aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude reaction was re-solved in Et_2O (15 mL) and THF (5 mL) and a 30% aq. H_2O_2 solution (9.0 mL, 79.40 mmol) was added in portions at 0°C with continuous stirring. The mixture was allowed to warm to room temperature and Et_2O (50 mL) was added 0.5 h later. It was washed with saturated aq. Na_2CO_3 (50 mL) and this aqueous fraction was re-extracted with Et_2O (2×30 mL). The combined organic layers were washed with 2N HCl (25 mL), saturated aq. Na_2SO_3 (25 mL) and brine (25 mL). After drying the organic phase with anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure a crude (1.90 g, 5.65 mmol, 94%), formed by a mixture of **4a** and **b** in a 55:45 ratio (according to the GC analysis), was obtained. An aliquot sample (300 mg) of this residue was flash chromatographed (eluent: H/E 6:4) to afford pure **4a** (140 mg) and **4b** (115 mg).

From the aqueous phase obtained after washing the H_2O_2-treated mixture with saturated aq. Na_2CO_3, Ph_2Se_2 (2.52 g, 56%) was recovered following the procedure described in Ref. 41.

3.2.1. Methyl 8α-hydroxy-labd-13*Z*-en-15-oate (4a). Colorless crystals; R_t 20.65; mp 131.9–133.7°C (hexane); $[\alpha]_D=+34.6°$ (*c* 0.68); IR (neat) ν 3529, 1086, 1075 (OH), 1703, 1237, 1175, 1145 (COOMe), 1641, 857 (C=C); ^1H NMR δ 0.74 (3H, s, Me_β-4), 0.76 (3H, s, Me-10), 0.84 (3H, s, Me_α-4), 1.15 (3H, s, Me-8), 1.83 (1H, dt, *J*=12.4, 3.1 Hz, H_β-7), 1.88 (3H, d, *J*=1.4 Hz, Me-13), 2.14–2.26 (1H, m, H-12), 2.84-2.97 (1H, m, H′-12), 3.30 (1H, br s, OH), 3.64 (3H, s, OMe), 5.63 (1H, br s, H-14); ^{13}C NMR δ 39.30 (C-1), 18.45 (C-2), 41.94 (C-3), 33.21 (C-4), 56.03 (C-5), 20.22 (C-6), 43.15 (C-7), 73.88 (C-8), 61.52 (C-9), 38.79 (C-10), 24.19 (C-11), 37.44 (C-12), 161.96 (C-13), 115.09 (C-14), 166.98 (C-15), 25.62 (C-16), 24.13 (C-17), 33.32 (C-18), 21.41 (C-19), 15.45 (C-20), 51.03 (OMe); MS *m/z* 336 (M^+, 0.3%), 319 (M^+-OH, 0.2), 318 (M^+-H_2O, 0.2), 304 ($M^+-OH-Me$, 6), 303 (M^+-H_2O-Me, 0.6), 289 (304^+-Me, 0.9), 276 ($M^+-HCOOMe$, 4), 266 (11), 243 (276^+-H_2O-Me, 1), 205 (3), 191 (3), 177 (8), 163 (3), 149 (6), 137 (6), 123 (11), 114 (26), 110 (25), 95 (32), 81 (38), 69 (61), 55 (74), 43 (100). HRMS (M^+), found 336.2700, $C_{21}H_{36}O_3$ requires 336.2664.

3.2.2. Methyl 8α-hydroxy-labd-13*E*-en-15-oate (4b). Colorless crystals (lit.[38]); R_t 21.66; mp 88.0–89.0°C (hexane); $[\alpha]_D=+13.7°$ (*c* 0.71); IR (neat) ν 3553, 1074 (OH), 1714, 1224, 1149 (COOMe), 1646, 854 (C=C); ^1H NMR δ 0.77 (6H, s, Me_β-4, Me-10), 0.85 (3H, s, Me_α-4), 1.13 (3H, s, Me-8), 1.85 (1H, dt, *J*=12.0, 3.1 Hz, H_β-7), 2.15 (3H, d, *J*=1.2 Hz, Me-13), 3.67 (3H, s, OMe), 5.67

(1H, br s, H-14); ^{13}C NMR δ 39.72 (C-1), 18.40 (C-2), 41.89 (C-3), 33.22 (C-4), 56.07 (C-5), 20.57 (C-6), 44.33* (C-7), 74.18 (C-8), 61.37 (C-9), 39.16 (C-10), 23.53 (C-11), 44.71* (C-12), 161.35 (C-13), 114.70 (C-14), 167.35 (C-15), 19.09 (C-16), 23.98 (C-17), 33.36 (C-18), 21.46 (C-19), 15.40 (C-20), 50.76 (OMe) (* these signals may be interchanged); MS *m/z* 304 (M^+−OH–Me, 0.6%), 303 (M^+−H_2O–Me, 0.6), 289 (304^+−Me, 0.4), 276 (M^+−HCOOMe, 1), 266 (3), 243 (276^+−H_2O–Me, 1), 205 (3), 191 (9), 177 (12), 163 (2), 149 (5), 135 (7), 123 (10), 114 (21), 109 (19), 95 (34), 82 (59), 69 (56), 55 (70), 43 (100).

3.3. 8α,13-Epoxy-14,15-dinorlabd-12-ene (6)

To a stirred solution of crude **4a/b** (205 mg, 0.60 mmol, 55:45 ratio) in acetone (15 mL) was added a mixture of $KMnO_4$ (333 mg, 2.20 mmol) and anhydrous $MgSO_4$ (290 mg) at room temperature. After stirring for 0.5 h the reaction mixture was filtered over Celite and the solvent evaporated under reduced pressure at room temperature. The residue was solved in Et_2O (20 mL) and washed with H_2O (3×10 mL). After drying the organic layer with anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure at room temperature, a residue (164 mg) was obtained which was composed of **5** and **6** in a 5:2 ratio, according to the ^{1}H NMR spectrum (GC analysis only showed a single peak at R_t 15.08). ^{1}H NMR data corresponding to **5** (lit.[22]): δ 0.79 (3H, s, Me$_\beta$-4), 0.80 (3H, s, Me-10), 0.86 (3H, s, Me$_\alpha$-4), 1.15 (3H, s, Me-8), 1.87 (1H, dt, J=12.2, 3.1 Hz, H$_\beta$-7), 2.13 (3H, s, Me-13), 2.57 (1H, ddd, J=17.8, 7.8, 5.7 Hz, H-12), 2.68 (1H, dt, J=17.8, 7.8 Hz, H′-12).

That residue was flash chromatographied (eluent: H/E 8:2) to yield pure **6** (107 mg, 0.41 mmol, 68%) as a pale yellow oil (lit.[22]); R_t 15.08; mp 34.0–36.0°C (MeOH); $[\alpha]_D$=+1.2° (*c* 0.95); IR (neat) ν 3054, 1683 (C=C), 1127 (C–O–C); ^{1}H NMR δ 0.82 (6H, s, Me$_\beta$-4, Me-10), 0.88 (3H, s, Me$_\alpha$-4), 1.16 (3H, s, Me-8), 1.68 (3H, br s, Me-13), 1.94 (1H, dt, J=12.3, 3.2 Hz, H$_\beta$-7), 4.43 (1H, br s, H-12); ^{13}C NMR δ 39.29 (C-1), 18.56 (C-2), 41.91 (C-3), 33.14 (C-4), 56.17 (C-5), 19.74 (C-6), 41.12 (C-7), 76.17 (C-8), 52.43 (C-9), 36.66 (C-10), 18.26 (C-11), 94.54 (C-12), 147.83 (C-13), 20.43 (C-16), 20.07 (C-17), 33.43 (C-18), 21.55 (C-19), 15.00 (C-20); MS *m/z* 263 (M^++1, 7%), 262 (M^+, 35), 247 (M^+−Me, 8), 244 (7), 229 (M^+−Me–H_2O, 16), 219 (3), 204 (4), 201 (5), 191 (42), 177 (25), 163 (5), 149 (9), 135 (16), 123 (29), 109 (73), 95 (50), 81 (55), 69 (32), 55 (40), 43 (100).

3.4. Reaction of 4a/b with FAM to give formate esters 7a and b

A sample (3.8 mL, 29.00 mmol) of formic acid–acetic anhydride mixture (FAM), prepared from Ac_2O and formic acid as described in the literature,[46] was slowly added for 15 min to a mixture of **4a** and **b** (1.90 g, 5.65 mmol, 55:45 ratio) at 10°C. After stirring for 48 h at room temperature, water (50 mL) was added and the mixture extracted with Et_2O (3×50 mL). The combined organic layers were washed with 2N HCl (50 mL), saturated aq. Na_2CO_3 (50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to yield a residue (1.91 g, 5.25 mmol, 93%) formed by a mixture of **7a** and **b** in a 55:45 ratio, according to the ^{1}H NMR spectrum. An aliquot sample (453 mg) of this residue was purified by flash chromatography (eluent: H/E 8:2) to afford pure **7a** (161 mg) and **7b** (131 mg).

3.4.1. Methyl 8α-formyloxy-labd-13*Z*-en-15-oate (7a).

Colorless crystals; mp 58.0–59.6°C (hexane); $[\alpha]_D$=−12.7° (*c* 1.02); IR (KBr) ν 1728, 1193 (OOCH), 1705, 1241, 1171 (COOMe), 1649, 875 (C=C); ^{1}H NMR δ 0.77 (3H, s, Me$_\beta$-4), 0.82 (3H, s, Me-10), 0.86 (3H, s, Me$_\alpha$-4), 1.49 (3H, s, Me-8), 1.88 (3H, d, J=1.4 Hz, Me-13), 2.53 (1H, dt, J=12.5, 3.3 Hz, H$_\beta$-7), 2.59–2.76 (2H, m, H-12), 3.65 (3H, s, OMe), 5.60 (1H, br s, H-14), 8.04 (1H, s, OOCH); ^{13}C NMR δ 39.36* (C-1), 18.35 (C-2), 41.80 (C-3), 33.13 (C-4), 55.52 (C-5), 20.01 (C-6), 39.32* (C-7), 89.08 (C-8), 58.91 (C-9), 39.53 (C-10), 24.10 (C-11), 36.13 (C-12), 160.49 (C-13), 115.44 (C-14), 166.53 (C-15), 25.16 (C-16), 21.24 (C-17), 33.29 (C-18), 21.42 (C-19), 15.69 (C-20), 50.78 (OMe), 160.65 (OOCH) (* these signals may be interchanged); MS *m/z* 364 (M^+, 0.1%), 349 (M^+−Me, 0.2), 319 (M^+−OOCH, 12), 318 (M^+−HCOOH, 4), 304 (M^+−HCOOMe, 1), 303 (318^+−Me, 4), 287 (M^+−HCOOH–OMe, 4), 259 (318^+−COOMe, 4), 205 (12), 192 (21), 177 (19), 149 (11), 136 (21), 121 (23), 109 (27), 95 (39), 81 (41), 69 (55), 55 (70), 41 (100). HRMS (M^+), found 364.2615, $C_{22}H_{36}O_4$ requires 364.2614.

3.4.2. Methyl 8α-formyloxy-labd-13*E*-en-15-oate (7b).

Colorless crystals; mp 89.1–91.0°C (hexane); $[\alpha]_D$=−18.9° (*c* 1.06); IR (KBr) ν 1716, 1184 (OOCH), 1716, 1218, 1148 (COOMe), 1651, 854 (C=C); ^{1}H NMR δ 0.79 (3H, s, Me$_\beta$-4), 0.84 (3H, s, Me-10), 0.88 (3H, s, Me$_\alpha$-4), 1.50 (3H, s, Me-8), 2.17 (3H, s, Me-13), 2.60 (1H, dt, J=12.1, 3.1 Hz, H$_\beta$-7), 3.69 (3H, s, OMe), 5.67 (1H, br s, H-14), 8.01 (1H, s, OOCH); ^{13}C NMR δ 39.50 (C-1), 18.21 (C-2), 41.72 (C-3), 33.07 (C-4), 55.52 (C-5), 19.95 (C-6), 39.37 (C-7), 89.00 (C-8), 58.46 (C-9), 39.50 (C-10), 23.87 (C-11), 43.62 (C-12), 160.77 (C-13), 114.83 (C-14), 167.23 (C-15), 19.02 (C-16), 21.03 (C-17), 33.22 (C-18), 21.36 (C-19), 15.60 (C-20), 50.74 (OMe), 160.28 (OOCH); MS *m/z* 364 (M^+, 0.5%), 349 (M^+−Me, 0.7), 319 (M^+−OOCH, 5), 318 (M^+−HCOOH, 4), 304 (M^+−HCOOMe, 1), 303 (318^+−Me, 7), 287 (M^+−HCOOH–OMe, 5), 259 (318^+−COOMe, 3), 205 (17), 192 (62), 177 (40), 149 (17), 137 (24), 123 (38), 109 (41), 95 (57), 81 (67), 69 (77), 55 (84), 41 (100). HRMS (M^+), found 364.2606, $C_{22}H_{36}O_4$ requires 364.2614.

3.5. 8α-Formyloxy-14,15-dinorlabdan-13-one (8)

To a stirred solution of crude **7a/7b** (286 mg, 0.78 mmol, 55:45 ratio) in acetone (18 mL) was added a mixture of $KMnO_4$ (632 mg, 4.00 mmol) and anhydrous $MgSO_4$ (600 mg) at room temperature. After stirring for 0.75 h the reaction mixture was worked-up, as for compound **6**, to afford crude **8** (214 mg, 0.68 mmol, 88%). An aliquot sample (107 mg) of crude **8** was purified by flash chromatography (eluent: H/E 4:6) to give pure **8** (89 mg) as a colorless solid; mp 66.0–67.4°C (hexane); $[\alpha]_D$=−22.3° (*c* 1.01); IR (KBr) ν 1722, 1198, 1165 (OOCH), 1696 (CO); ^{1}H NMR δ 0.79 (3H, s, Me$_\beta$-4), 0.86 (3H, s, Me-10), 0.88

(3H, s, Me$_\alpha$-4), 1.52 (3H, s, Me-8), 2.13 (3H, s, Me-13), 2.43–2.69 (3H, m, H$_\beta$-7, H-12), 8.02 (1H, s, OOCH); ^{13}C NMR δ 39.48 (C-1), 18.17 (C-2), 41.67 (C-3), 33.04 (C-4), 55.50 (C-5), 19.87 (C-6), 39.48 (C-7), 88.99 (C-8), 57.95 (C-9), 39.48 (C-10), 19.26 (C-11), 46.37 (C-12), 208.98 (C-13), 29.78 (C-16), 21.03 (C-17), 33.21 (C-18), 21.32 (C-19), 15.42 (C-20), 160.28 (OOCH); MS *m/z* 263 (M^+-OOCH, 0.7%), 262 (M^+-HCOOH, 0.9), 245 (M^+-OOCH–H_2O, 7), 244 (M^+-HCOOH–H_2O, 1), 229 (262^+-H_2O–Me, 2), 219 (262^+-CH_3CO, 0.2), 204 (262^+-Me–CH_3CO, 3), 191 (2), 177 (2), 161 (1), 149 (1), 136 (6), 121 (5), 109 (6), 95 (8), 81 (8), 67 (10), 55 (13), 43 (100). HRMS (M^+-HCOOH), found 262.2296, $C_{18}H_{30}O$ requires 262.2297.

3.6. 12-Acetoxy-8α-formyloxy-13,14,15,16-tetranorlabdane (9)

Method A. *m*-Chloroperoxybenzoic acid (348 mg, 2.02 mmol, prepared from technical grade *m*-CPBA by washing with saturated aq. $NaHCO_3$) was added to a solution of crude **8** (529, 1.72 mmol) in CH_2Cl_2 (20 mL), and the mixture was left to stand in the dark at room temperature for 12 days. During this period, additional portions of the enriched *m*-CPBA (170 mg, 0.99 mmol) were added every day to complete the reaction. The mixture was washed with 10% aq. Na_2SO_3 (3×15 mL), saturated aq. Na_2CO_3 (3×15 mL) and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford crude **9** (532 mg, 1.64 mmol, 96%). An aliquot sample (148 mg) of this crude was purified by flash chromatography (eluent: H/E 6:4) to afford pure **9** (93 mg) as a colorless oil; $[\alpha]_D=-23.8°$ (*c* 0.93) IR (neat) ν 1738, 1248, 1235 (OAc), 1719, 1200, 1179 (OOCH); ^{1}H NMR δ 0.79 (3H, s, Me$_\beta$-4), 0.85 (3H, s, Me-10), 0.88 (3H, s, Me$_\alpha$-4), 1.52 (3H, s, Me-8), 2.04 (3H, s, OAc), 2.64 (1H, dt, J=12.5, 3.3 Hz, H$_\beta$-7), 4.10 (2H, t, J=7.8 Hz, H-12), 8.00 (1H, s, OOCH); ^{13}C NMR δ 39.27* (C-1), 18.18 (C-2), 41.66 (C-3), 33.08 (C-4), 55.46 (C-5), 19.88 (C-6), 39.41* (C-7), 88.36 (C-8), 54.91 (C-9), 39.03 (C-10), 24.69 (C-11), 65.74 (C-12), 20.91† (C-17), 33.20 (C-18), 21.34 (C-19), 15.49 (C-20), 160.15 (OOCH), 170.96 (OAc), 20.99† (OAc) (*,† these signals may be interchanged); MS *m/z* 278 (M^+-HCOOH, 8%), 219 (M^+-HCOOH–OAc, 7), 218 (M^+-HCOOH–HOAc, 34), 203 (218^+-Me, 22), 190 (6), 175 (9), 161 (6), 149 (12), 136 (59), 123 (28), 109 (37), 94 (70), 81 (36), 69 (23), 55 (19), 43 (100).

Method B. *m*-Chloroperoxybenzoic acid (135 mg, 0.78 mmol, prepared from technical grade *m*-CPBA by washing with saturated aq. $NaHCO_3$) and a phosphate buffer (2.5 mL, pH 7.4) were added to a stirred solution of **8** (92 mg, 0.30 mmol) in CH_2Cl_2 (2.5 mL). The reaction flask was protected from light and the suspension cooled to 0°C. Then, trifluoroacetic acid (0.025 mL, 0.32 mmol) was added, and the mixture allowed to stir at room temperature for 4 days. An additional portion of enriched *m*-CPBA (135 mg, 0.78 mmol) was added for complete consumption of the starting material. Finally, the mixture was worked-up as in Method A to afford **9** (78 mg, 0.24 mmol, 81%).

3.7. 13,14,15,16-Tetranorlabdan-8α,12-diol (10)

A mixture of crude **9** (525 mg, 1.62 mmol) and 10% methanol KOH (10 mL, 17.90 mmol) was stirred at room temperature for 10 min. The crude reaction was concentrated under reduced pressure to remove MeOH, resuspended in water (50 mL) and extracted with Et_2O (3×40 mL). The combined organic extracts were washed with brine (2×20 mL), dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to yield crude **10** (244 mg, 0.96 mmol, 59%). An aliquot sample (130 mg) of this crude product was flash-chromatographied (eluent: E) to afford pure **10** (95 mg) as a colorless solid (lit.[22,37]); R_t 17.10; mp 130.6–132.2°C (hexane); $[\alpha]_D=-15.8°$ (*c* 1.01); IR (KBr) ν 3270, 1054, 1033 (OH); ^{1}H NMR δ 0.79 (6H, s, Me$_\beta$-4, Me-10), 0.87 (3H, s, Me$_\alpha$-4), 1.19 (3H, s, Me-8), 1.90 (1H, dt, J=12.2, 3.2 Hz, H$_\beta$-7), 3.44 (1H, dt, J=10.1, 6.9 Hz, H-12), 3.77 (1H, dt, J=10.1, 4.3 Hz, H′-12); ^{13}C NMR δ 39.31 (C-1), 18.38 (C-2), 41.86 (C-3), 33.24 (C-4), 55.99 (C-5), 20.42 (C-6), 44.15 (C-7), 72.94 (C-8), 59.23 (C-9), 38.94 (C-10), 27.82 (C-11), 63.98 (C-12), 24.56 (C-17), 33.38 (C-18), 21.45 (C-19), 15.29 (C-20); MS *m/z* 254 (M^+, 0.3%), 239 (M^+-Me, 4), 236 (M^+-H_2O, 3), 221 (M^+-H_2O–Me, 8), 195 (21), 177 (45), 165 (8), 151 (22), 139 (10), 123 (15), 109 (44), 95 (50), 81 (41), 69 (61), 55 (57), 43 (100).

3.8. 8α,12-Epoxy-13,14,15,16-tetranorlabdane (Ambrox® (1))

A mixture of crude **10** (244 mg, 0.96 mmol) and *p*-toluenesulfonic acid monohydrate (113 mg, 0.58 mmol) in $MeNO_2$ (17 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O (65 mL), washed with saturated aq. $NaHCO_3$ (2×20 mL) and brine (20 mL). The organic layer was dried with anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure to afford a residue (230 mg), which after flash chromatography (eluent: H/E 7:3) yielded pure **1** (170 mg, 0.72 mmol, 75%) as a colorless solid (lit.[20]); R_t 13.49; mp 73.6–75.4°C (hexane); $[\alpha]_D=-24.6°$ (*c* 0.68); IR (KBr) ν 1069, 1007, 979, 916 (C–O–C); ^{1}H NMR δ 0.83 (3H, s, Me$_\beta$-4), 0.84 (3H, s, Me-10), 0.88 (3H, s, Me$_\alpha$-4), 1.09 (3H, s, Me-8), 1.94 (1H, dt, J=11.4, 3.1 Hz, H$_\beta$-7), 3.82 (1H, q, J=8.2 Hz, H-12), 3.91 (1H, td, J=8.2, 4.3 Hz, H′-12); ^{13}C NMR δ 39.72* (C-1), 18.37 (C-2), 42.41 (C-3), 33.03 (C-4), 57.23 (C-5), 20.62 (C-6), 39.93* (C-7), 79.84 (C-8), 60.10 (C-9), 36.16 (C-10), 22.60 (C-11), 64.92 (C-12), 21.10 (C-17), 33.55 (C-18), 21.10 (C-19), 15.00 (C-20) (* these signals may be interchanged); MS *m/z* 236 (M^+, 1%), 221 (M^+-Me, 62), 203 (M^+-Me–H_2O, 3), 177 (2), 165 (1), 151 (2), 137 ($C_{10}H_{17}^+$, 22), 121 (6), 109 (12), 97 (51), 81 (38), 67 (50), 55 (62), 41 (100).

3.9. Cyclization reactions of 10 with *p*-TsOH

A mixture of **10** and *p*-toluenesulfonic acid monohydrate in $MeNO_2$ or CH_2Cl_2 was stirred at room or high temperature for different period of times (Table 1). Aliquot samples were diluted with Et_2O, washed with saturated aq. $NaHCO_3$ and brine. The organic layers were dried over anhydrous Na_2SO_4 and directly monitored by GC.

3.9.1. 8β,12-Epoxy-13,14,15,16-tetranorlabdane (*iso*-Ambrox (11)). R_t 12.82; MS *m/z* 221 (M^+-Me, 55%), 203 (M^+-Me-H_2O, 3), 177 (3), 165 (1), 147 (2), 137 ($C_{10}H_{17}{}^+$, 17), 121 (6), 109 (7), 97 (28), 81 (20), 67 (24), 55 (42), 41 (100).

3.9.2. 13,14,15,16-Tetranorlabd-8-en-12-ol (12). R_t 14.68; MS *m/z* 236 (M^+, 3%), 221 (M^+-Me, 5), 203 (M^+-Me-H_2O, 2), 191 ($M^+-C_2H_5O$, 9), 177 (6), 163 (4), 151 (4), 135 (6), 121 ($C_9H_{13}{}^+$, 13), 107 (20), 95 (31), 81 (20), 69 (25), 55 (49), 41 (100).

3.9.3. 13,14,15,16-Tetranorlabd-7-en-12-ol (13). R_t 15.07; MS *m/z* 236 (M^+, 2%), 221 (M^+-Me, 0.9), 203 (M^+-Me-H_2O, 0.6), 192 (1), 191 ($M^+-C_2H_5O$, 1), 177 (2), 163 (0.6), 149 (2), 136 (3), 124 ($C_9H_{16}{}^+$, 15), 112 (M^+-124, 27), 109 (124^+-Me, 66), 94 (22), 81 (112^+-OMe, 32), 69 (25), 55 (56), 41 (100).

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